CASE REPORT

Extraskeletal myxoid chondrosarcoma of the heart and review of current literature

H.L. Geyer MD and N. Karlin MD

ABSTRACT

Extraskeletal myxoid chondrosarcoma (EMS) is a rare oncologic phenomenon characterized by chondroid and neurogenic differentiation in extraskeletal locations. These tumours represent fewer than 2.5% of all soft-tissue sarcomas and are most commonly found in the lower extremities, limb girdles, distal extremities, and trunk. Their presence in cardiac tissue is exceedingly unusual; just a single case of EMS metastatic to the heart has been reported, and no cases of primary cardiac EMS are known.

Here, we report the case of a 26-year-old man who presented to his physician with a chest wall mass. Further evaluation led to the discovery of a large intracardiac mass with multiple end-organ growths. Complete work-up of this patient included cardiac biopsy, echocardiography, magnetic resonance imaging, positron-emission tomography, computed tomography, and fluorescence in situ hybridization studies for the translocation involving the EWSR1 gene locus (22q12). Results of the foregoing studies confirmed the diagnosis of EMS, but the origin of this patient’s tumours remains elusive and the contention between a primary cardiac source and cardiac metastasis has yet to be resolved.

This article describes the histopathology, immunohistochemistry, and chromosomal aberrations common to EMS, together with the common presenting features, natural history, and prognosis.

KEY WORDS

Myxoid chondrosarcoma, extraskeletal, cardiac, primary, metastatic

1. CASE DESCRIPTION

In February 2007, a 26-year-old man presented to his primary care physician with a history of a 30-minute episode of light-headedness, vertigo, ataxia, and left-sided extremity numbness. Cerebral magnetic resonance imaging (MRI) revealed an inferior infarct of the right posterior cerebral artery. A transesophageal echocardiogram showed no evidence of a cardiac structural abnormality, thrombus, or mass. The patient was placed on anti-platelet medication without further workup.

In September 2007, the patient returned with new-onset left flank pain, intermittent back pain, and visual disturbances. He also described the development of a mass in his left chest wall which had been increasing in size over the year. Physical exam confirmed the presence of a chest wall mass, and a harsh grade 3/6 systolic murmur was heard over the pulmonary valve on cardiac examination. Computed tomography (CT)–guided biopsy revealed a 2.0×3.5-cm low- to intermediate-grade myxoid sarcoma. The neoplastic cells were negative for wide-spectrum cytokeratin, S-100 protein, desmin, and smooth muscle actin.

Transesophageal echo revealed a large (2.4×6.3-cm) mass of the right ventricular outflow tract, prolapsing into the pulmonary artery, with attachment at the crista supraventricularis; a right ventricular systolic pressure of 65 mmHg; and a 1.7×1-cm mass on the right aortic valve cusp resulting in severe aortic regurgitation. Gadolinium-enhanced MRI of the brain demonstrated 5 intracranial masses within the right temporal lobe, the left occipital lobe, the right thalamus, the left frontal lobe, and the right parietal cortex.

On combined positron-emission tomography/CT (PET–CT) staging, diffuse uptake was seen in the lateral aspect of the left 5th and 6th ribs, consistent with the patient’s known tumour. Intense focal uptake was also evident within the right gluteus maximus, and faint activity was observed adjacent to the right second rib and the proximal jejenum. A focal cold defect was identified within the right atrium, extending into the main pulmonary artery.

The patient was referred to cardiothoracic surgery for immediate removal of the right ventricular mass and excision of the native aortic valve. Pathology results from cardiac specimens confirmed a myxoid sarcoma, consistent with extraskeletal myxoid chondrosarcoma (EMS). A biopsy of the right mesial temporal region confirmed metastatic disease. The patient was referred to oncology for further treatment.
Past medical history of this patient was notable for asthma and hemorrhoids. His medications on admission included albuterol, tiotropium, beclomethasone, montelukast, docusate sodium, and dibucaine. The patient had been employed as an electronics technician, and he denied tobacco or excessive alcohol exposure. His family history included a grandmother with kidney cancer. Basic laboratory values, including a complete blood count and chemistry and lipid panels, remained unremarkable throughout his evaluation.

The patient underwent radiosurgery and whole-brain radiation. Palliative systemic chemotherapy included doxorubicin and ifosfamide. After 3 cycles, the ifosfamide was discontinued because of renal tubular acidosis. The tumour initially regressed over a period of 7 months, but central nervous system disease progressed, resulting in spinal cord compression. The patient was subsequently switched to gemcitabine for 1 cycle, but he experienced rapid progression of his disease, predominantly within the abdominal cavity. He was then given doxorubicin, but unfortunately had no response. Given his clinical course and prognosis, the patient ultimately opted for palliative care. The patient died 17 months from the time of diagnosis.

1.1 Histologic Findings

The cardiac excisional biopsy specimens revealed loosely approximated cardiac tissue with positive surgical margins. Specimens included an aortic valve mass (3.1×2.2×0.1 cm), a right ventricular outflow tract mass (aggregating 13.5×7.8×0.7 cm), and a right ventricular outflow tract tumour attachment margin.

Microscopically, proliferation of multilobular tumour divided by thin fibrous septa (Figure 1) was seen. The lobules consisted of a rich myxoid and chondromyxoid stroma mixed with neoplastic cells (Figure 1). The cells interconnected to form characteristic cords, clusters, cribiform arrays, and spindle-cell patterns (Figures 2 and 3). The neoplastic cells possessed a modest amount of eosinophilic, and occasionally vacuolated, cytoplasm with uniform round to oval nuclei (Figure 3). The chromatin was evenly distributed, with small nucleoli. Focal hyalinized cytoplasmic globules were present. Mitotic activity averaged 10 per 10 high-power fields. Some areas, particularly at the periphery, showed higher cellularity with focal necrosis (Figure 4).

1.2 Immunohistochemical Findings

Immunohistochemical studies were performed on paraffin sections of the cardiac mass using antibodies against antigens for keratin, human smooth muscle actin, actin, CD31, CD34, S-100, chromogranin, vimentin, and synaptophysin. These tumour cells expressed only vimentin, although synaptophysin was
focally and weakly positive as well. Other markers for epithelial (keratin, epithelial membrane antigen (EMA)), muscular (actin, desmin, myogenin), and vascular (CD31, CD34) tumour were all negative. Fluorescence in situ hybridization studies for translocations involving the EWSR1 gene locus (22q12) were negative. Further studies to evaluate for other possible chromosomal translocations associated with EMS tumours were not performed.

2. DISCUSSION

Extraskeletal myxoid chondrosarcoma is an extremely rare clinical entity characterized by chondroid and neurogenic differentiation in extraskeletal locations. The incidence of EMS is less than 2.5% among all soft-tissue sarcomas. The presence of EMS in cardiac tissue is exceedingly unusual.

The debate as to whether the cardiac tumour in this case was primary or metastatic has yet to be resolved. If indeed primary, it would be the first case reported in the literature. If metastatic, it would be the second—the first case having been described by Banfic and colleagues in 2001. Statistically, tumours metastatic to the heart are 20–40 times more common than primary cardiac tumours, which typically occur at an incidence of 0.0017%–0.0019%, with most emanating from carcinoma of the bronchus, melanoma, breast cancer, and lymphoma. The most frequent methods of spread are movement through the coronary arteries and lymphatic channels, or direct extension. Isolated metastasis to the myocardium without involvement of the pericardium, the most frequently affected location, would be unusual. Given that background, the possibility of this tumour being a primary remains under consideration. On average, 75% of all primary heart tumours are benign; the remaining 25% are malignant. Of the malignant tumours, 75% are sarcomas. The most common primary cardiac sarcomas include angiosarcomas (37%), malignant fibrous histiocytomas (24%), leiomyosarcomas (9%), and rhabdomyosarcomas (7%).

Stout and Verner first described EMS in 1953 in their account of 4 unique tumour cases. The variable histologic and morphologic appearance in EMS often makes an accurate diagnosis challenging. Three categories of EMS tumour are posited: classic, mesenchymal, and myxoid (the rarest being the myxoid variety). Extraskeletal myxoid chondrosarcomas traditionally behave less aggressively than do other more common forms of chondrosarcomas; as such, they are deemed “low grade.” Their histologic characteristics often lead to a misdiagnosis as the myxoid variant of another sarcoma such as liposarcoma, mesenchymal chondrosarcoma, or malignant fibrous histiocytoma, or as parachordoma or another myxoid soft-tissue tumour. However, detailed pathology analyses have shown that EMS is a distinct clinical entity characterized by cytogenetic and molecular aberrations.

The histogenesis of EMS remains elusive. Morphologic features have suggested a cartilaginous origin. Those features include the presence of chondroitin-4 and -6 sulphate and keratin sulphate—both major components of the cartilaginous matrix. The EMS cellular structure is also similar to that of chondrocytes, including abundant and dilated rough endoplasmic reticulum, glycogen granules, cytoplasmic microvilli, and well-developed Golgi complexes. The extracellular matrix is composed of ultrastructures characteristic of hyaline cartilage, including amorphous granulofilamentous material, tropocollagen, and the occasional mature collagen fibrils. In rare instances, type II collagen has reportedly been detected. However, the suggestion of a cartilaginous origin has been brought into question because, unlike chondrocytes, EMS tumours lack overt cartilage formation, occur usually in soft tissues, and do not calcify. In addition, most do not express S-100, a protein consistently present in neoplastic chondrocytes.

The present debate raised the possibility of derivation from primitive mesenchymal cells. The concept of a mesenchymal phenotype is supported by the presence of interstitial collagen types I, III, VI, and vimentin found in various samples of EMS. Other suggestions regarding origin have included fibroblast metaplasia and embryonic arrests of the cartilaginous matrix. More recently, evidence has been presented supporting a neural or neuroendocrine differentiation by immunohistochemical findings, including expression of synaptophysin (up to 72% of all EMS cases) and the presence of neuroendocrine granules. Neural crest cells have the potential to give rise to a variety of terminally differentiated cells including neurons, cartilage, bone, and dermis. Extraskeletal myxoid chondrosarcoma may therefore represent a neuroectodermal derivation of pluripotent neural crest cells. The uncertainty regarding EMS derivation has led the World Health
Organization (WHO), in its classification of tumours of soft tissue and bone, to provisionally classify EMS as a tumour of uncertain differentiation.

Typically, EMS affects patients 35 years of age or older, with more than half of all cases occurring in patients in and beyond their fifth decade. However, cases have occasionally been reported in children and adolescents. On average, men are more commonly affected than women. Approximately 66% of these tumours originate in the lower extremities and limb girdles, followed by the distal extremities (23%) and trunk (13%). Unusual locations have included the mediastinum, retroperitoneum, distal upper extremities, and the intracranial cavity.

Grossly, EMS tumours may present at various stages of development, depending on the location. They are often grey-white in hue, with a gelatinous, easily friable structure. Diameter at presentation ranges from 6 cm to 13 cm, with a typical multinodular or nodular configuration, a poorly defined fibrous capsule, and well-defined margins. Because of their predilection for hemorrhage, these tumours may be mistaken for hematomas.

Histologically, tumour cells cluster into lobules divided by thin, fibrous septa of variable thickness. Cells are short, spindle, or oval, with hyperchromatic or vesicular nuclei and occasionally vacuolated cytoplasm. Grooved or cleaved nuclei suggest chondroid differentiation are occasionally observed. They occasionally possess unipolar or bipolar cytoplasmic processes. Mitotic activity is rare. They may be arranged in clusters, cords, or a laccelike structure. The cytoplasm may range from transparent to granular, and cells are surrounded by a myxoid matrix. The matrix may be inherently more dense than the cells themselves and may lack discernable cartilaginous histology.

On immunohistochemical staining, EMS tumours stain strongly positive for vimentin in up to 70% of cases. They are also often weakly positive for S-100 (20%–50% of cases). Surprisingly, recent studies have shown EMS to stain positive for neural or neuroendocrine markers such as neuron-specific enolase, protein gene product 9.5, and synaptophysin. Staining with Ki-67 may highlight the myxomatous regions in 2%–5% of the sample and the cellular areas in 9%–15% of the sample. Cytokeratin and EMA are typically negative.

One unique characteristic of EMS is chromosomal aberrations and the resultant fusion (chimeric) genes. The most common of these chimeric combinations is the chromosomal translocation t(9;22)(q22;q12), found in up to 60% of EMS tumours. Other translocations include t(9;17)(q22;q11) and t(9;15)(q22;q21). The translocation t(9;22)(q22;q11) has also recently been discovered and is associated with EMS tumours producing neuroendocrine secretions. The patient in our case was screened for the t(9;22)(q22;q12) aberration only, and results were negative.

Currently, no specific laboratory, echocardiographic, or physical exam findings will suggest EMS over other more common cardiac tumours. The initial differential diagnosis is therefore often broad and may include myxomas, papillary fibroelastomas, hemangiomas, teratomas, rhabdomyomas, thrombus, and infective endocarditis.

Most patients with intracardiac masses are symptomatic on presentation. Common symptoms of intracardiac tumours include dyspnea, chest pain, chronic heart failure, palpitations, fever, myalgia, and constitutional symptoms of weakness, anemia, and fever. Symptoms are typically the result of 1 of 4 complications: obstruction to blood flow, valvular dysfunction, embolism, and local invasion leading to arrhythmia and pericardial effusions. In our case, the patient had suffered an occlusive cerebrovascular event of cryptogenic origin 7 months before the discovery of his cardiac tumour. Although the echo performed during the initial evaluation of the cerebrovascular event was unremarkable, the concept of small embolic cardiac fragments being the origin of the cerebrovascular event is quite plausible. As previously discussed, later evaluations showed multiple end-organ tumours, further reinforcing the possibility of embolic origins from a primary cardiac source.

As with most intracardiac tumours, EMS is best evaluated with a combination of chest radiography, electrocardiography, CT, echocardiography, and MRI. As established in this case report, EMS may grow to large proportions before detection. The chest radiographs may show cardiomegaly or mediastinal widening. Calcifications are not characteristic of EMS tumours and, if observed, may suggest alternative causation. Echocardiography may prove especially important by providing an estimate of intraoperative risk and by identifying valve involvement, ventricular function, intracavitary masses, and extension of the tumour. Because of a high degree of tissue resolution, MRI and CT may provide valuable information about tumour extension and differentiation between tumour and thrombus. All patients over the age of 40 with intracardiac masses should be evaluated with cardiac catheterization to evaluate for conduction delays, obstruction, and pericardial effusions. The electrocardiogram may show nonspecific findings, such as right or left ventricular hypertrophy, atrial fibrillation, or paroxysmal atrial tachycardia.

Treatment for EMS depends on histology. Tumours with low cellularity and higher proportions of myxoid matrix may be treated with local excision. Tumours with higher levels of cellularity and lower proportions of myxoid matrix are best treated with radical surgery. As with all intracardiac tumours, evidence of severe obstruction or intractable arrhythmia requires immediate tumour resection, if feasible. Depending on the level of pleomorphism, adjuvant radiotherapy or chemotherapy may help to prevent
local recurrence. To date, no studies have identified the most efficacious chemotherapy for EMS.

Long-term follow-up is essential because metastasis and local recurrence may appear up to 20 years after initial treatment. Previous observations have estimated 10-year survival rates in the 70%–78% range, with a local recurrence rate of 48% and a metastasis rate of 31%–46%. The rate of remote dissemination is higher in patients with primary local recurrences (86%) than in those in whom the primary tumour does not recur after initial removal (19%). The growth pattern of EMS is slower and less aggressive than that seen in other subsets of chondrosarcoma. Studies have shown that the factors most closely associated with clinical behaviour include age at presentation, primary tumour site, and presence or absence of metastases. Other studies have shown adverse clinical outcomes based on histologic characteristics including mitotic activity and cellularity. Ironically, some studies have suggested that none of these variables affect prognosis. Regardless, surveillance for recurrence of EMS is the most effective way to prevent future complications and to promote optimal quality of life.

3. CONCLUSIONS

Much has yet to be discovered about this rare and unique tumour. Studies to identify the histogenesis of EMS and its preferred molecular targets will ultimately lead to better diagnostic and therapeutic options. We hope that as research in this field progresses, greater knowledge will be gained to more effectively prevent, diagnose, and manage this exceptional malignancy.

4. CONFLICT OF INTEREST DISCLOSURES

All authors declare that no financial conflict of interest exists.

5. REFERENCES


Correspondence to: Holly L. Geyer, Mayo Clinic–Arizona, 13400 E Shea Boulevard, Scottsdale, Arizona 85254 U.S.A.

E-mail: Geyer.holly@mayo.edu